(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 February 2001 (22.02.2001)

PCT

(10) International Publication Number
WO 01/12176 A2

(51) International Patent Classification[7]: A61K 31/16

(21) International Application Number: PCT/EP00/07917

(22) International Filing Date: 8 August 2000 (08.08.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
99116026.8 16 August 1999 (16.08.1999) EP

(71) Applicant *(for all designated States except US)*: SANOFI-SYNTHELABO [FR/FR]; 174, avenue de France, F-75013 Paris (FR).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: ROSENZWEIG, Pierre [FR/FR]; 117, avenue de Choisy, F-75013 Paris (FR).

(74) Agent: THOURET-LEMAITRE, Elisabeth; Sanofi-Synthelabo, 174, avenue de France, F-75013 Paris (FR).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/12176 A2

(54) Title: USE OF MONOAMINE OXIDASE INHIBITORS FOR THE MANUFACTURE OF DRUGS INTENDED FOR THE TREATMENT OF OBESITY

(57) Abstract: The present invention relates to the use of reversible selective inhibitors of monoamine oxidase A (MAO-A), reversible selective inhibitors of monoamine oxidase B (MAO-B) or reversible mixed inhibitors of MAO-A and MAO-B in the manufacture of drugs intended for the treatment of obesity.

USE OF MONOAMINE OXIDASE INHIBITORS FOR THE MANUFACTURE OF DRUGS INTENDED FOR THE TREATMENT OF OBESITY

The present invention relates to the use of monoamine oxidase inhibitors in the manufacture of drugs intended for the treatment of obesity.

Obesity is a major health problem in western societies and its prevalence is increasing. As described in Cheryl P. Kordik and Allen B. Reitz, *J. Med. Chem.* (1999), **42**(2), 181-201, reviewing the various known strategies to treat obesity, obesity is a "chronic condition characterized by overabundance of adipose tissue" which "correlates with risks such as high blood pressure, coronary heart disease, diabetes, altered steroid metabolism, gallstones and certain forms of cancer".

Obesity is a multifactorial disease and its treatment requires multidisciplinary approaches. The treatment includes diet, exercise, behavior change, pharmacotherapy, and surgery. In the medical treatment of obesity, different approaches may be considered. Drugs may decrease energy intake (central or peripheral action), decrease energy storage, increase energy expenditure, or have a combination of different actions. A few compounds are currently available in some countries. These include sibutramine (a serotonin and norepinephrine reuptake inhibitor) and orlistat (a pancreatic lipase inhibitor).

Disorders linked to disturbances of eating behavior include bulimia nervosa and anorexia nervosa. Bulimia nervosa is characterized by compulsive overeating binges followed by inappropriate compensatory behaviors such as vomiting, fasting, excessive exercise, and misuse of diuretics or laxatives to maintain a desired weight. This eating behavior is associated with comorbid psychopathology, and can result in serious medical complications (e.g., dental erosion, esophagitis, gastrointestinal irritation, electrolyte imbalances).

The treatment of bulimia nervosa differs from the treatment of common forms of obesity. It may include cognitive-behavioral therapy, group therapy, family therapy, individual psychotherapy, and pharmacotherapy (e.g., antidepressants). Since bulimia nervosa is associated with marked alteration in monoaminergic systems (Benedetti M.S. et al.: "monamine oxidase: from physiologicology to the design and clinical application of reversible inhibitors", *Advances in drug research* (1992), **23**, 65-125), a number of monoamine oxidase inhibitors have been tried in bulimia nervosa as reported in Liebowitz M.R. et al.: "reversible and irreversible

monamine oxidase inhibitors in other psychiatric disorders", *Acta Psychiatrica Scandinavica supplementum* (1990), **360**, 29-34; Kennedy S.H. et al.: "is there a role for selective monoamine oxidase inhibitor therapy in blimia nervosa ? A placebo-controlled trial of brofaromine", *Journal of clinical psychopharmacology* (1993), **13**(6), 415-22; Priest R.G. et al.: "reversible and selective inhibitors of monoamine oxidase A in mental and other disorders", *Acta Psychatrica Scandinavica* (1995), **91**, Suppl. 386, 40-43; Wittal M.C. et al.: "Boulimia nervosa: A meta-analysis of phsychosocial and pharmacological treatments", *Behaviour therapy* (1999), **30**, 117-135.

It has now been found that reversible selective inhibitors of monoamine oxidase A (MAO-A), reversible selective inhibitors of monoamine oxidase B (MAO-B) or reversible mixed inhibitors of MAO-A and MAO-B have activity in decreasing body weight of obese patients. They may act by decreasing energy intake and/or increasing energy expenditure.

Accordingly, the present invention relates to the use of reversible selective inhibitors of MAO-A, reversible selective inhibitors of MAO-B or reversible mixed inhibitors of MAO-A and MAO-B for the manufacture of drugs intended for the treatment of obesity.

The invention therefore further relates to a method of treating obesity by administering to a patient in need of such treatment a therapeutically effective amount of a reversible selective inhibitor of MAO-A, a reversible selective inhibitor of MAO-B or a reversible mixed inhibitor of MAO-A and MAO-B.

In fact, candidates for treatment may be men and women suffering from obesity or overweight.

Among reversible MAO-A inhibitors, befloxatone, moclobemide, brofaromine, phenoxathine, esuprone, befol, RS 8359 (Sankyo), T794 (Tanabe), KP 9 (Krenitsky, USA), E 2011 (Eisei), toloxatone, pirlindole, amiflamine, sercloremine and bazinaprine may be cited.

These compounds are known and their preparation are described in the art.

Among reversible selective inhibitors of MAO-B, lazabemide, milacemide, caroxazone and IFO may be cited.

Among reversible selective inhibitors of MAO-A, reversible selective inhibitors of MAO-B or reversible mixed inhibitors of MAO-A and MAO-B the following compounds may also be cited:

- compounds disclosed in patent application EP 699680, i.e. 3,3a,4,5-tetrahydro-1*H*-oxazolo[3,4-a]quinolin-1-one derivatives and particularly [3(*S*),3a(*S*)]-3-methoxymethyl-7-(4,4,4-trifluoro-3(*R*)-hydroxybutoxy)-3,3a,4,5-tetrahydro-1*H*-oxazolo[3,4-a]quinolin-1-one and [3(*S*),3a(*S*)]-3-methoxymethyl-7-[4,4,4-trifluorobutoxy]-3,3a,4,5-tetrahydro-1*H*-oxazolo[3,4-a]quinolin-1-one,

- compounds disclosed in patent application WO 96/38444, i.e. oxazolidin-2-one derivatives and particularly (*S*)-5-methoxymethyl-3-[6-(4,4,4-trifluorobutoxy)-1,2-benzisoxazol-3-yl]oxazolidin-2-one,

- compounds disclosed in patent application WO 97/13768, i.e. oxazolidin-2-one derivatives and particularly (*R*)-5-(methoxymethyl)-3-[6-(4,4,4-trifluorobutoxy)benzofuran-3-yl]oxazolidin-2-one and (*R*)-5-methoxymethyl-3-(6-cyclopropylmethoxybenzofuran-3-yl)oxazolidin-2-one.

Befloxatone or 3-[4-(4,4,4-trifluoro-3(*R*)-hydroxybutoxy)phenyl]5(*R*)-methoxymethyl-2-oxazolidinone, which is known for its antidepressive and mild anxiolytic activity is particularly prefered as reversible MAO-A inhibitor. It is a reversible monamine oxidase inhibitor with both a very high affinity for the A isoform (MAO-A) and great selectivity versus the B isoform (MAO-B), which does not affect reuptake of noradrenaline (NA), serotonine (5-HT) or dopamine (DA).

Its chemical synthesis is described in EP 424244.

As reversible MAO-B inhibitor (*S*)-5-methoxymethyl-3-[6-(4,4,4-trifluorobutoxy)-1,2-benzisoxazol-3-yl]oxazolidin-2-one is preferred.

As reversible mixed inhibitor of MAO-A and MAO-B [3(*S*),3a(*S*)]-3-methoxymethyl-7-[4,4,4-trifluorobutoxy]-3,3a,4,5-tetrahydro-1*H*-oxazolo[3,4-a]quinolin-1-one, (*R*)-5-(methoxymethyl)-3-[6-(4,4,4-trifluorobutoxy)benzofuran-3-yl]oxazolidin-2-one and (*R*)-5-methoxymethyl-3-(6-cyclopropylmethoxybenzofuran-3-yl)oxazolidin-2-one are preferred.

The active substance according to the invention can be administred to patients in a variety of pharmaceutical forms well-known in the art and particularly in the form of compositions formulated for administration by the oral, injectable, transdermal or rectal route.

For oral administration, said compositions can take the form of tablets, dragees or capsules prepared by the conventional techniques using known carriers and excipients, such as binding agents, fillers, lubricants and desintegration agents; they can also be in form of solutions, syrups or suspensions.

For administration by the injectable route, the compositions according to the invention may be in the form of injectable solutions, suspensions or emulsions containing an acceptable oily or aqueous liquid carrier.

For transdermal administration, the composition can take the form of a patch wherein the drug can be encompassed in a gel, solution, ointment or cream.

For rectal administration, the compositions may be in the form of suppositories containing the conventional bases for suppositories.

The percentage of active compound in such compositions may be varied so that a suitable dosage is obtained. The dosage administered to a particular patient is determined by the clinician according to the mode of administration, the age and weight of the patient and the patients response. Unit dosage forms may be administered in a single dose or in multiple divided doses to provide the appropriate daily dosage.

The daily dosage for example of befloxatone can range from about 2.5 to 40 mg, preferably from about 10 to 20 mg.

The following examples relating to pharmacological data and a galenic formulation illustrate the present invention.

Example 1

FEEDING BEHAVIOUR IN FASTED RATS

Male Wistar rats (Iffa-Credo) were individually housed in polycarbonate cages (48x26.5x21.5 cm) in a temperature- and humidity-controlled animal colony room (20±2°C) with a 12-hour light dark cycle (7 a.m. - 7 p.m.). At least 1 week before the experiment, every animal was often handled and administered saline by oral route in order to avoid stress. Food and water were available ad libitum, and all testing was done in the home cage. Rats were fasted for 24 hour before testing and allowed free access to water. In the morning of the test day, rats were first assigned to either a treatment or a control group then weighed and administered drug or vehicle p.o. (10.30 a.m.) and returned to their home cage. Thirty minutes later, a measured quantity of food (RMM, Harlan Ibérica) was made available to the animals. The food intake is calculated every hour until 6 hours after the drug

administration. (WO95/11894, Gehlert et al., *J. Pharmacol. Exp. Ther.* (1998), **287**, 122-127).

Grams of food consumed by the treated animals every hour was compared to food consumed by the control animals using one-way analysis of variance with a Newman-Keuls' test.

Table

Effect of befloxatone on food consumption during light period (7 a.m.-7 p.m.) in fasted rats (24 hours). Recording and access to food 11 a.m.-2 p.m.

Group		Food intake (g)		
		0 - 1 hour	0 - 2 hours	0 - 3 hours
Control (vehicle p.o.)		7.56 ± 0.33	11.0 ± 1.33	11.84 ± 1.37
Befloxatone (3 mg/kg p.o.)		5.12 ± 0.78*	7.94 ± 1.20	10.86 ± 0.94

*p< 0.05 vs control (ANOVA test)

Example 2

FEEDING BEHAVIOUR IN FED RATS

Male Wistar rats (Iffa-Credo) were individually housed into a temperature- and humidity-controlled animal room (20±2°C) with a 12-hour light dark cycle (4.30 a.m. - 4.30 p.m.). in polycarbonate special cages with transducers connected to MacLab system. This enables to record the food consumption at every moment of day (light/dark phase). A measured quantity of food (RMM, Harlan Ibérica) is placed on the cage just before dark onset.

In order to avoid any kind of stress that could have an effect on their behaviour, every rat is administered saline and put in the cage at least 1 or 2 days before the test. The food consumption is recorded, without interruption, during these

days. Once the animal is used to the cage, the test compound or vehicle are administered, by oral route.

Grams of food consumed by the animals during the first 4 hours after drug administration was compared to food consumed by the control animals over the same period of time, using one-way analysis of variance with a Newman-Keuls' test.

Table

Effect of 7 days treatment with befloxatone (10 mg/kg/day, p.o.) on food consumption during dark period (4.30 p.m. - 4.30 a.m.) in fed male Wistar rats

Days of treatment	Food intake (g)	
	Control vehicle p.o. (n=7)	Befloxatone 10 mg/kg/day, p.o. (n=6)
1	3.98 ± 0.63	3.03 ± 0.40
2	5.91 ± 0.85	3.31 ± 1.00
3	7.95 ± 0.68	5.32 ± 0.69*
4	7.35 ± 0.57	6.12 ± 0.50
5	8.75 ± 0.76	6.10 ± 0.59*
6	9.69 ± 0.98	6.98 ± 0.61*
7	10.1 ± 0.74	6.95 ± 0.75*

*$p < 0.05$ vs control (ANOVA test)

These results show that in the model using **fasted rats**, befloxatone (3 mg/kg p.o.) inhibits food intake by about 25% during the first hour after administration of the drug, and in the model of **fed rats** with recording of food consumption in the dark, befloxatone (10 mg/kg p.o.), once a day for 7 days, inhibits as from the third day, food intake during the first four hours after drug administration.

Exemple 3

BODY WEIGHT GAIN STUDY IN OBESE ZUCKER RATS

Befloxatone was studied in obese (fa/fa) Zucker rats, a genetic animal model of obesity.

Experimental procedure

Animals

Genetically obese Zucker (fa/fa) male rats and lean (+/?) male littermates were purchased from IFFA CREDO (France).

One week before the start of the experiment, animals were individually housed in polycarbonate cages (45 x 30 x 20 cm), with food (A04 standard diet, UAR, France) and water *ad libitum*, in a room with controlled temperature (23°C ± 1°C), in a reversed light-dark cycle (lights off at 9 h 00, on at 21 h 00) and total refresh air (12-15 times per hour). Obese and lean rats were 13 weeks old when used and weighed 380-430 g and 280-330 g respectively.

Drug

Befloxatone was suspended in an aqueous solution with 0.5 % Tween 80, and administered orally in a volume of 5 ml/kg.

Protocol

- Animals were treated p.o., once daily (at 9 h 00) for 5 weeks.

Four groups of obese (fa/fa) rats were administered vehicle or befloxatone at the doses of 1, 3 and 10 mg/kg/day.

Two groups of lean rats were administered vehicle or befloxatone (10 mg/kg/day).

- Daily food intake and body weight were recorded (at 8 h 00).

Results

Results are expressed as mean ± SEM for each treatment group. A two-way

ANOVA with repeated measures on time factor was conducted on food intake and cumulative body weight gain across weeks of befloxatone administration.

In obese rats, befloxatone induced a decrease (but non significant) of food intake over the treatment period. In lean rats this effect was more pronounced as food intake was significantly decreased on weeks 1 and 4.

A 5-week chronic treatment with befloxatone induced a dose related reduction of body weight gain in obese rats. This effect was significant from the first week of treatment for the dose of 10 mg/kg/day. In lean rats befloxatone (10mg/kg/day) also induced a similar and significant reduction of body weight gain. At the end of the treatment, weight gain was reduced by 26% ($p<0.05$) and 24% ($p<0.01$) in obese and lean rats respectively.

Example 4

ORAL FORMULATION

Befloxatone	2.5 mg	0.125 kg
Maize starch	5 mg	0.250 kg
Lactose monohydrate	83 mg	4.150 kg
Povidone K29/32	5 mg	0.250 kg
Crospovidone	4 mg	0.200 kg
Magnesium stearate	0.5 %	0.025 kg
size 3 gelatine capsule		

The befloxatone and approximately 10% of the lactose (415 g), were premixed for 10 minutes using a Turbula mixer. The mixture was then transferred to a Diosna mixer-granulator. The remainder of the lactose, the maize starch, the povidone, and half the crospovidone were added and mixed for 3 minutes. A sufficient quantity of water was added (13%) and the mixture granulated for 3 minutes. The granulate was dried in a ventilated oven and calibrated at 0.63 mm. The rest of the crospovidone, plus the magnesium stearate was added to the resulting granulate, and the whole was mixed using a Turbula mixer for 10 minutes, and then filled into size 3 capsules to a unit mass of 100 mg.

Claims

1. Use of a reversible selective inhibitor of monoamine oxidase A, reversible selective inhibitor of monoamine oxidase B or a reversible mixed inhibitor of monoamine oxidase A and B for the manufacture of drugs intended for the treatment of obesity.

2. Use of a reversible mixed inhibitor of monoamine oxidase A and B according to claim 1.

3. The use according to claim 2 wherein the reversible mixed inhibitor of monoamine oxidase A and B is chosen among [3(*S*),3a(*S*)]-3-methoxymethyl-7-[4,4,4-trifluorobutoxy]-3,3a,4,5-tetrahydro-1*H*-oxazolo[3,4-a]quinolin-1-one, (*R*)-5-(methoxymethyl)-3-[6-(4,4,4-trifluorobutoxy)benzofuran-3-yl]oxazolidin-2-one and (*R*)-5-methoxymethyl-3-(6-cyclopropylmethoxybenzofuran-3-yl)oxazolidin-2-one.

4. Use of a reversible selective inhibitor of monoamine oxidase B according to claim 1.

5. The use according to claim 4 wherein the reversible selective monoamine oxidase B is chosen among lazabemide, milacemide, caroxazone and IFO.

6. The use according to claim 4 wherein the reversible selective monoamine oxidase B is (*S*)-5-methoxymethyl-3-[6-(4,4,4-trifluorobutoxy)-1,2-benzisoxazol-3-yl]oxazolidin-2-one.

7. Use of a reversible selective inihibtor of monoamine oxidase A according to claim 1.

8. The use according to claim 7 wherein the reversible selective inhibitor of monoamine oxidase A is chosen among befloxatone, moclobemide, brofaromine, phenoxathine, esuprone, befol, RS 8359 (Sankyo), T794 (Tanabe), KP 9 (Krenitsky,

USA), E 2011 (Eisei), toloxatone, pirlindole, amiflamine, sercloremine and bazinaprine.

9. The use according to claim 7 wherein the reversible selective inhibitor of monoamine oxidase A is befloxatone.

10. The use according to claim 9 wherein the dosage amount of befloxatone is from about 2.5 to 40 mg per day.

11. The use according to claim 10 wherein the amount of befloxatone to be administered is from 10 to 20 mg.

12. The use according to any of claims 1 to 11 wherein the inhibitor of monoamine oxidase is intended for administration by the oral, injectable, transdermal or rectal route.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 February 2001 (22.02.2001)

PCT

(10) International Publication Number
WO 01/12176 A3

(51) International Patent Classification[7]: A61K 31/39, 31/16, 31/35, 31/42, 31/425, 31/44, 31/445, 31/47, 31/50, 31/505, 31/535

(21) International Application Number: PCT/EP00/07917

(22) International Filing Date: 8 August 2000 (08.08.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
99116026.8 16 August 1999 (16.08.1999) EP

(71) Applicant *(for all designated States except US)*: **SANOFI-SYNTHELABO** [FR/FR]; 174, avenue de France, F-75013 Paris (FR).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: **ROSENZWEIG, Pierre** [FR/FR]; 117, avenue de Choisy, F-75013 Paris (FR).

(74) Agent: **THOURET-LEMAITRE, Elisabeth**; Sanofi-Synthelabo, 174, avenue de France, F-75013 Paris (FR).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
21 March 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/12176 A3

(54) Title: USE OF MONOAMINE OXIDASE INHIBITORS FOR THE MANUFACTURE OF DRUGS INTENDED FOR THE TREATMENT OF OBESITY

(57) Abstract: The present invention relates to the use of reversible selective inhibitors of monoamine oxidase A (MAO-A), reversible selective inhibitors of monoamine oxidase B (MAO-B) or reversible mixed inhibitors of MAO-A and MAO-B in the manufacture of drugs intended for the treatment of obesity.

INTERNATIONAL SEARCH REPORT

Interr ɔnal Application No
PCT/EP 00/07917

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/39 A61K31/16 A61K31/35 A61K31/42 A61K31/425
A61K31/44 A61K31/445 A61K31/47 A61K31/50 A61K31/505
A61K31/535

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, EMBASE, MEDLINE, BIOSIS, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 13768 A (LECLERC ODILE ;JEGHAM SAMIR (FR); PUECH FREDERIC (FR); SYNTHELABO) 17 April 1997 (1997-04-17) cited in the application abstract page 34, line 7,8 page 41, paragraph 2 ---	1-4,12
X	WO 96 38444 A (SYNTHELABO ;JEGHAM SAMIR (FR); PUECH FREDERIC (FR); BURNIER PHILIP) 5 December 1996 (1996-12-05) cited in the application abstract page 24, line 1 -page 25, line 19; example 7 --- -/--	1,2,4,6, 12

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 October 2001	02/11/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	A. Jakobs

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 699 680 A (SYNTHELABO) 6 March 1996 (1996-03-06) cited in the application table 1,entry 52-57 page 24, line 1 -page 25, line 19; example 7	3
X	DE 30 15 360 A (MERRELL TORAUDE & CO) 6 November 1980 (1980-11-06) page 11, paragraph 2 -page 12, paragraph 2; example 7 page 22, paragraph 2 - paragraph 2; example 7	1,2,4,7, 12
X	US 3 466 236 A (HOSTETTLER HANS U) 9 September 1969 (1969-09-09) column 1, line 68-71 - paragraph 2; example 7	1,2,4,7, 12
X	US 3 153 092 A (A. BURGER) 13 October 1964 (1964-10-13) column 1, line 10-36 - paragraph 2; example 7	1,2,4,7, 12
X	ZAHM P. ET AL: "Twelve-month oral toxicity study of lazabemide in dogs." JAPANESE PHARMACOLOGY AND THERAPEUTICS, (1994) 22/SUPPL. 11 (105-143)., XP000879086 abstract paragraph 2; example 7	1,2,4,5, 7,12
X	LIEBOWITZ M R ET AL: "Reversible and irreversible monoamine oxidase inhibitors in other psychiatric disorders." ACTA PSYCHIATRICA SCANDINAVICA. SUPPLEMENTUM, (1990) 360 29-34. REF: 43, XP000879199 abstract paragraph 2; example 7 page 30, column 2, paragraph 3 -page 31, column 1, paragraph 2; example 7	1,2,4,7, 12
X	KENNEDY S H ET AL: "Is there a role for selective monoamine oxidase inhibitor therapy in bulimia nervosa? A placebo-controlled trial of brofaromine." JOURNAL OF CLINICAL PSYCHOPHARMACOLOGY, (1993 DEC) 13 (6) 415-22., XP000879189 abstract paragraph 2; example 7	1,2,4,8, 12

-/--

1

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	PRINGUEY D. ET AL: "'Antidepressants!. ANTIDEPRESSEURS." REVUE DU PRATICIEN, (15 JAN 1999) 49/2 (209-214)., XP000879200 abstract paragraph 2; example 7; table 1 page 209, column 2, paragraph 2 - paragraph 2; example 7; table 1 ---	1,2,4,8, 12
X	THIEL A.: "'Is psychopharmacotherapy necessary in anorexia and bulimia nervosa?!. SIND PSYCHOPHARMAKA FUR DIE BEHANDLUNG DER ANOREXIA UND BULIMIA NERVOSA NOTWENDIG?." PPMP PSYCHOTHERAPIE PSYCHOSOMATIK MEDIZINISCHE PSYCHOLOGIE, (1997) 47/9-10 (332-345)., XP000879185 abstract paragraph 2; example 7; table 3 ---	1,2,4,8, 12
X	BENEDETTI M.S. ET AL: "Monoamine oxidase: From physiology and pathophysiology to the design and clinical application of reversible inhibitors." ADVANCES IN DRUG RESEARCH, (1992) 23/- (65-125)., XP000879188 page 90, paragraph 2 -page 91, paragraph 1; example 7; table 3 page 98, paragraph 1 -page 103, paragraph 2; example 7; table 3 page 108, paragraph 1 - paragraph 2; example 7; table 3 ---	1,2,4,8, 12
X	PRIEST, R. G. (1) ET AL: "Reversible and selective inhibitors of monoamine oxidase A in mental and other disorders." ACTA PSYCHIATRICA SCANDINAVICA, (1995) VOL. 91, NO. SUPPL. 386, PP. 40-43., XP000879201 abstract paragraph 2; example 7; table 3 ---	1,2,4,8, 12
X	WHITTAL M.C. ET AL: "Bulimia nervosa: A meta-analysis of psychosocial and pharmacological treatments." BEHAVIOR THERAPY, (1999) 30/1 (117-135)., XP000879168 abstract paragraph 2; example 7; table 1 --- -/--	1,2,4,8, 12

INTERNATIONAL SEARCH REPORT

Interr ›nal Application No
PCT/EP 00/07917

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	REYNAERT C. ET AL: "Do new antidepressants influence body weight ? Comparing moclobemide to fluoxetine." EUROPEAN NEUROPSYCHOPHARMACOLOGY, (1993) 3/3 (354)., XP000879190 page 354, paragraphs 5,6 - paragraph 2; example 7; table 1 _____	1,2,4,8, 12

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1,2,4,7,12 relate to a use/product defined by reference to a desirable characteristic or property, namely reversible selective or reversible mixed monoamine oxidase A and/or B inhibitors.

The claims cover the use of all products/compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such products/compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product/compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the products/compounds specifically mentioned in the claims with due regard to the general idea underlying the present invention(s).

A compound or group of compounds is not sufficiently defined only by its pharmacological parameters or properties: for a fully valid definition of a compound or a group of compounds, a structural definition is needed. A complete search is virtually impossible because it is not exhaustively known which chemical compounds are comprised by the scope of the claims encompassing reversible selective or reversible mixed monoamine oxidase A and/or B inhibitors in general.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

ormation on patent family members

Interr ›nal Application No
PCT/EP 00/07917

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9713768 A	17-04-1997	FR 2739856 A1	18-04-1997
		FR 2751651 A1	30-01-1998
		FR 2751653 A1	30-01-1998
		AU 7135996 A	30-04-1997
		EP 0891358 A1	20-01-1999
		WO 9713768 A1	17-04-1997
		JP 11513400 T	16-11-1999
		US 5969146 A	19-10-1999
		ZA 9608568 A	13-05-1997
WO 9638444 A	05-12-1996	FR 2734820 A1	06-12-1996
		FR 2734821 A1	06-12-1996
		AT 184005 T	15-09-1999
		AU 699367 B2	03-12-1998
		AU 6128896 A	18-12-1996
		BR 9608896 A	29-06-1999
		CA 2223011 A1	05-12-1996
		CN 1191534 A	26-08-1998
		CZ 9703784 A3	15-04-1998
		DE 69604071 D1	07-10-1999
		DE 69604071 T2	06-04-2000
		DK 835254 T3	27-03-2000
		EP 0835254 A1	15-04-1998
		ES 2138346 T3	01-01-2000
		WO 9638444 A1	05-12-1996
		GR 3031710 T3	29-02-2000
		HU 9901349 A2	30-08-1999
		IL 118542 A	06-12-2000
		JP 11507330 T	29-06-1999
		NO 975530 A	02-02-1998
		NZ 310487 A	28-05-1999
		PL 323673 A1	14-04-1998
		SK 161497 A3	06-05-1998
		US 5843975 A	01-12-1998
		ZA 9604563 A	12-12-1996
EP 0699680 A	06-03-1996	FR 2724171 A1	08-03-1996
		AT 190311 T	15-03-2000
		AU 687591 B2	26-02-1998
		AU 3041595 A	21-03-1996
		CN 1128763 A ,B	14-08-1996
		CZ 9502262 A3	13-03-1996
		DE 69515402 D1	13-04-2000
		DE 69515402 T2	19-10-2000
		DK 699680 T3	21-08-2000
		EP 0699680 A1	06-03-1996
		ES 2145886 T3	16-07-2000
		FI 954141 A	06-03-1996
		GR 3033554 T3	29-09-2000
		HU 73435 A2	29-07-1996
		IL 115276 A	06-12-1998
		JP 8099881 A	16-04-1996
		NO 953458 A	06-03-1996
		NZ 272920 A	25-03-1998
		PL 310273 A1	18-03-1996
		PT 699680 T	31-08-2000
		RU 2141482 C1	20-11-1999
		SI 699680 T1	31-10-2000

INTERNATIONAL SEARCH REPORT

ormation on patent family members

Interr nal Application No
PCT/EP 00/07917

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0699680 A		SK 108995 A3	05-06-1996
		US 5641785 A	24-06-1997
		ZA 9507414 A	15-04-1996
DE 3015360 A	06-11-1980	AU 5550780 A	30-10-1980
		BE 882104 A4	01-07-1980
		DE 3015360 A1	06-11-1980
		DE 3015373 A1	06-11-1980
		DK 180980 A	27-10-1980
		ES 490440 D0	01-04-1981
		ES 8104183 A1	01-07-1981
		FR 2457277 A2	19-12-1980
		GB 2048875 A	17-12-1980
		IT 1143941 B	29-10-1986
		JP 55145641 A	13-11-1980
		NL 8002418 A	28-10-1980
		NO 801210 A	27-10-1980
		SE 8003117 A	27-10-1980
		ZA 8001117 A	25-02-1981
US 3466236 A	09-09-1969	NONE	
US 3153092 A	13-10-1964	GB 950388 A	26-02-1964